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Practitioner's Docket No. 61190(50221) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Simon McEwen Group No.:
Application No.: 10/820099
Filed: April 7, 2004 Examiner:
For: *THERAPEUTIC COMPOSITION FOR AUTOIMMUNE CONDITIONS*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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Country: Great Britain

Application Number: 0307989.4

Filing Date: April 7, 2003

Country:

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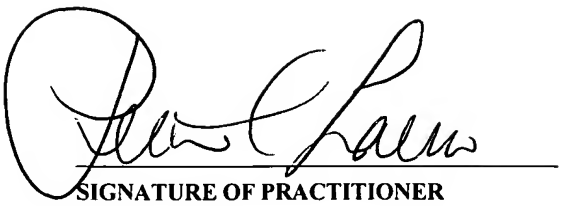

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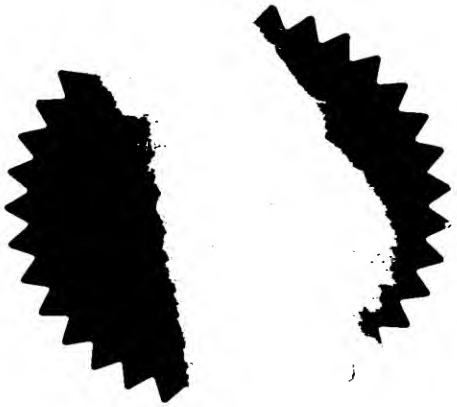

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1. Your reference — JMH/6654

2. Patent application number *(The Patent Office will fill in this part)* — 07 APR 2003 — 0307989.4

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

McEwen Laboratories Ltd.
12 Horseshoe Park
Pangbourne
Berkshire
RG8 7JW

08606220001
Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — U.K

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7/5/3
Om

4. Title of the invention — "Therapeutic Composition"

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Stevens Hewlett & Perkins
1 St Augustines Place
Bristol BS1 4UD
UK

Parents ADP number *(if you know it)* — 1545002

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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Signature Stevens, Hewlett & Perkins Date 07/04/03

Stevens Hewlett & Perkins

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THERAPEUTIC COMPOSITION

This invention relates to a therapeutic composition. More particularly, the present invention relates to a therapeutic composition for the treatment, alleviation or prophylaxis of autoimmune conditions.

Autoimmunity is present to some extent in everyone and is usually harmless. However, autoimmunity can cause a broad range of human illnesses, known collectively as autoimmune diseases, disorders or conditions. Autoimmune conditions occur when there is progression from benign autoimmunity to pathogenic autoimmunity when a misdirected immune response occurs in an individual in which the immune system attacks the body itself rather than a foreign body or a xenobiotic. This progression is determined by genetic influences as well as environmental triggers.

Immune reactions are nearly always characterised by inflammation, which indicates an underlying repair process. However, in the case of autoimmune diseases the inflammation may be chronic, causing tissue damage. For example, in rheumatoid arthritis chronic inflammation causes characteristic damage to joints and cartilage. The precise origin and pathophysiological processes of these diseases are not fully known.

Current treatments for autoimmune conditions are generally concerned with pain management, the administration of anti-inflammatory drugs, replacing lost substance (for example, the provision of insulin in diabetes mellitus) or the administration of immunosuppressant. These treatments are generally systemic rather than local.

While these approaches may temporarily alleviate the conditions, or reduce their progress, they often act to directly counteract the actual physical state or effect rather than to remove, reduce or alter the underlying cause or aetiology of the condition. For example, it is known that many autoimmune reactions involve a T-cell mediated response, it would therefore be beneficial to provide a treatment for autoimmune conditions which acts on this response.

Autoimmunity is evidenced by the presence of autoantibodies (antibodies directed against the body) and T cells which are reactive with host antigens.

Autoimmune conditions may be systemic, for example systemic lupus erythematosus, or organ specific, for example thyroiditis. Other examples of autoimmune conditions include Sjögren's syndrome, Hashimoto's thyroiditis, rheumatoid arthritis, juvenile (type 1) diabetes, polymyositis, scleroderma, Addison's disease, vitiligo, pernicious anaemia, glomerulonephritis, and pulmonary fibrosis.

It is an object of the present invention to provide a therapeutic composition which mediates an effect on an auto immune condition by acting on the underlying cause or causes of the condition. However, the present invention may additionally have an effect on the physical state or effect of the condition.

Accordingly, the present invention provides a therapeutic composition comprising an enzyme and an immunogen at a dose which provides a beneficial effect in an individual in need of treatment.

Advantageously, the composition of the present invention mediates a response which has an action on the underlying cause of the autoimmune condition, for example it may act to downregulate T-cell mediated reactions. Without wishing to be bound by theory, the present inventor believes that the immunogens of the present invention indirectly reduce T-cell activity by means of an action mediated via the Langerhans or the dendritic cells or by the thymus, which action redirects antigen sensitive lymphocytes towards regulatory function (e.g. IL-10 production) or redirects cell activity away from the target site of the immunogen.

The term "immunogen" as used herein is intended to define any substance capable of inducing an immune response. It is not intended that any of the properties of the immunogen, such as molecular weight, are to be restricted by this term.

In the description which follows, the present invention will be described with particular reference to the treatment of rheumatoid arthritis. However, the invention finds equal utility in the treatment of other disorders by the selection of an appropriate immunogen. For example, multiple sclerosis may be treated by the use of myelin basic protein as the immunogen, thyroiditis or

Hashimoto's disease may be treated using thyroid proteins as the immunogen, and diabetes mellitus may be treated using insulin or β -cell proteins as the immunogen. Additionally, mixtures or combinations of immunogens may be used, especially where a condition implicates or is associated with one or more immunogens.

Preferably, the enzyme used in the composition is a liver enzyme or a mucopolysaccharidase. More preferably, the enzyme is a glucuronidase and most preferably is a β-glucuronidase. Ideally, the β-glucuronidase is β-D-glucuronoside glucuronosohydrolase (Registry number EC 3.2.1.31). The source of the enzyme has been found to make no difference to the activity of the composition, provided that the enzyme is free from preservatives or sorbitol. Hence, it may be necessary to purify the enzyme to enable its use in the composition of the invention. Any method of purification may be used but it has been found to be convenient to use gel filtration chromatography or tangential flow filtration.

It is preferred that the enzyme is purified to a concentration of at least 20,000 Fishman units/mg and is present in the composition at a concentration of between 200 and 10,000 units/ml and ideally between 1,000 and 5,000 units/ml.

It has been found that contamination by other proteins, even at very low levels can affect the activity of the enzyme. It is therefore preferred that a stabiliser and/or activator is present in the composition. The stabiliser and/or activator is preferably an inert proteinaceous moiety, for example protamine sulphate or 1,10 diamino decane. Preferably, the stabiliser and/or activator is present at a concentration of up to 20 mg/l. Where the stabiliser and/or activator is protamine sulphate, it is preferably present at a concentration of between 1 and 10 mg/l, more preferably at a concentration of between 3 and 9 mg/l and ideally at about 6 mg/l (equivalent to 6µg/ml).

The composition may further comprise hydroxyl moieties. Preferably, the hydroxyl moieties are provided by polyols which contain at least two hydroxyl moieties and more preferably by sugars or diols which contain at least two hydroxyl moieties. The preferred source of the hydroxyl moieties is 1,3

cyclohexane diol. Preferably, the 1,3 cyclohexane diol is present at a concentration of up to 20 µg/l, more preferably the 1,3 cyclohexane diol is present at a concentration of between 0.1 and 10 µg/l and ideally at a concentration of 1µg/l. The stereochemistry of the 1,3 cyclohexane diol has been found not to adversely affect the present invention and hence either the *cis*, or *trans* forms or a racemic mixture may be used.

The composition is preferably buffered to neutral or an acid pH. More preferably, the composition is buffered to a pH of between 5 and 6.5 and ideally the composition is buffered to pH 5.9.

In the preferred embodiment of the invention where the composition is used in the treatment of rheumatoid arthritis the preferred immunogen is collagen or fragments, derivatives, conjugates, mimetics or other products thereof or which have a collagen-type structure or activity whether natural, synthetic or modified, regardless of source. The term "collagen" as used hereafter is intended to include such collagen products as above described. The collagen is preferably present in a solution. The collagen may be from any source but it is preferred that the collagen be free from preservatives or sorbitol or other additives. Hence, it may be necessary to purify the collagen to enable its use in the composition of the invention. Any method of purification may be used but it has been found to be convenient to use gel filtration chromatography or tangential flow filtration.

The concentration of collagen present in the composition may be of between 10 and 1×10^{15} molecules/ml. More preferably, the collagen present in the composition may be at a concentration of between 1×10^{4} and 1×10^{13} molecules/ml. Generally, the concentration of the collagen present in the composition will vary according to the dose required, it is therefore contemplated that three ranges of collagen dosed compositions will be made available, these will be vary in strength from high to low. Compositions in the high strength range will contain collagen at a concentration of the order of 1×10^{10} to 1×10^{15} molecules/ml, and more preferably will contain about 1×10^{12} to 1×10^{13} molecules/ml. Ideally the high strength composition will contain 2.5×10^{13} molecules/ml. For compositions in the mid-strength range, collagen will

preferably be present at a concentration of the order of 1×10^9 to 1×10^{13} molecules/ml, and more preferably will contain about 1×10^{10} to 1×10^{12} molecules/ml. Ideally the mid-strength composition will contain 2.5×10^{11} molecules/ml. For compositions in the low strength range, collagen will preferably be present at a concentration of the order of 1×10^2 to 1×10^8 molecules/ml, and more preferably will contain about 1×10^4 to 1×10^7 molecules/ml. Ideally the mid-strength composition will contain 2.5×10^5 molecules/ml.

Preferably, the composition further comprises a glycosaminoglycan or mixtures or combinations thereof. Any glycosaminoglycan can be used but it is preferred that the glycosaminoglycan be selected from the group comprising hyaluronate (D glucuronic acid N acetyl D glucosamine), chondroitin sulphate (D glucuronic acid N acetyl D galactosamine 1, 3, 4 or 6 sulphate), dermatan sulphate (D glucuronic acid or L iduronic acid N acetyl D galactosamine), keratan sulphate (D galactose N acetyl D glucosamine sulphate), and heparan sulphate (D glucuronic acid or L iduronic acid N acetyl D glucosamine). The most preferred glycosaminoglycan is chondroitin -6-sulphate.

The glycosaminoglycan is preferably present in the composition at a concentration of between 0.1 and 1.0 mg/ml, most preferably 0.5 mg/ml. Ideally the glycosaminoglycan is free from preservatives or sugars and to ensure this it may be necessary to purify the glycosaminoglycan before use. Convenient methods of purification include gel filtration chromatography or tangential flow filtration.

The composition of the invention may be administered in any conventional manner either systemically or locally, for example by oral-, parenteral-, intra-dermal-, topical-, rectal-, nasal- routes, by local injection or by transdermal infusion. At present it is preferred that the composition is administered by sub-cutaneous injection, preferably by intradermal injection, or as any form of trans-dermal infusion. It is not necessary for the composition to be administered locally to the region of autoimmunity, especially in rheumatoid arthritis, but it may be preferable to do so in other conditions in order to

minimise any contra-indications or to expedite an effect at a particular location.

In a preferred embodiment, the composition is prepared a short time before administration or even immediately prior to administration. In this embodiment the composition may be provided as two preparations, an enzyme preparation and a collagen preparation, which are introduced to one another and mixed prior to administration. In this embodiment, the enzyme solution contains the stabilised enzyme, the hydroxyl moiety and the enzyme in a buffered solution; all of which are present as described above. The collagen solution contains the collagen and the glycosaminoglycan, buffered as described above. Preferably, the composition as administered contains more collagen solution than enzyme solution, more preferably at least twice the amount of collagen solution (by volume) and ideally about 4 parts collagen solution to each part enzyme solution, by volume.

Accordingly, the present invention also provides a kit for preparing the composition of the invention, the kit comprising an enzyme solution and an immunogen solution, the two solutions being introduced to one another and allowed to admix prior to administration to an individual in need of treatment. The kit may be presented in the form of a multi-chambered or multi-barrelled dispenser such a syringe.

The composition of the present invention may preserved between formation and use. For example, the composition may be frozen, dried, freeze-dried, lyophilized, encapsulated or further preserved with a suitable chosen preservative which has little or no adverse effect on the *in vivo* activity of the composition or by any other preserving technique commonly used or known for pharmaceuticals. Where the composition is dried or freeze-dried or otherwise rendered solid, the composition may be formed into a tablet, capsule, lozenge or other solid dosage form for oral administration or reconstituted for use in a solution of liquid form, for example for injection. Where the composition is frozen, it may be convenient to freeze the composition or its components in dose unit amounts, optionally in a syringe, to facilitate use by the individual or medical practitioner.

Any pharmaceutically acceptable solvent may be used to produce the liquid form of the composition. Similarly, the usual binders, excipients, vehicles, and other standard dosage additives may be used in the composition of the invention.

The present invention also provides a method of treating or preventing autoimmune conditions, the method comprising the administration of a therapeutically effective amount of a composition comprising an enzyme and an immunogen to an individual in need of treatment.

The present invention further provides a method of treating, alleviating or preventing rheumatoid arthritis, the method comprising the administration of a therapeutically effective amount of a composition comprising β-glucuronidase and collagen to an individual in need of treatment.

The present invention also provides the use of a therapeutically effective amount of an enzyme and an immunogen in the preparation of a medicament for the treatment or prevention of autoimmune conditions.

In a further aspect the present invention also provides the use of a β-glucuronidase and collagen in the preparation of a medicament for the treatment of rheumatoid arthritis.

In a final embodiment, the present invention provides a composition comprising 0.5 – 2.5 mg/ml β-glucuronidase, 6 µg/ml protamine sulphate, 1µg/ml 1,3 cyclohexane diol, and 0.5 mg/ml chondroitin sulphate, buffered to pH 5.9 and further comprising either 2.5×10^{13}, 2.5×10^{11} or 2.5×10^{5} molecules/ml of collagen for use in the treatment of rheumatoid arthritis.

Embodiments of the invention will now be described with reference to the following examples which are provided by way of example only.

EXAMPLE 1

β-glucuronidase (EC 3.2.1.31) (obtained from the marine mollusc *Haliotis midae* (South African abalone) was purified by gel filtration chromatography to remove any preservatives or sorbitol present.

The purified β-glucuronidase was added to a buffered solution at pH 5.9 to give a final concentration of 1.5 mg/ml. 1,3 cyclohexane diol (Sigma, Poole, Dorset, UK) was added to a final concentration of 1µg/ml. Protamine sulphate BP was added, with stirring to prevent precipitation, to a final concentration of 6µg/ml.

Separately, natural collagen–type II was purified by gel filtration chromatography to remove any preservatives or sorbitol present.

The purified collagen was dissolved in a solution and buffered to pH 5.9 to give a final collagen concentration of 2.5×10^{13}. To this solution, chondroitin sulphate was added to give a final concentration of 0.5 mg/ml.

0.01ml of enzyme solution was introduced to 0.04ml of collagen solution and allowed to mix. The 0.05ml bolus of composition was used as an intradermal injection in an arthritis model in mouse. Paw weights and volumes were measured against control mice receiving vehicle only, collagen only or β-glucuronidase only.

CLAIMS

1. A therapeutic composition comprising an enzyme and an immunogen at a dose which provides a beneficial effect in an individual in need of treatment.

2. A composition according to claim 1, in which the enzyme is a liver enzyme or a mucopolysaccharidase.

3. A composition according to claim 1 or claim 2, in which the enzyme is a β-glucuronidase.

4. A composition according to claim 3, in which the β-glucuronidase is β-D-glucuronoside glucuronosohydrolase (Registry number EC 3.2.1.31).

5. A composition according to any one of the preceding claims, in which the enzyme is present at a concentration of between 200 and 10,000 Fishman units/ml.

6. A composition according to claim 5, in which, the enzyme is present at a concentration of between 1,000 and 5,000 units/ml.

7. A composition according to claim 5, in which the enzyme is present at a concentration of between 0.5 and 2.5 mg/ml.

8. A composition according to any one of the preceding claims, in which the composition further comprises a stabiliser and/or activator.

9. A composition according to claim 8, in which the stabiliser and/or activator is an inert proteinaceous moiety.

10. A composition according to claim 8 or claim 9, in which, the stabiliser and/or activator is protamine sulphate or 1,10 diamino decane.

11. A composition according to any one of claims 8 to 10, in which the stabiliser and/or activator is present at a concentration of up to 20 mg/l.

12. A composition according to any one of claims 8 to 10, in which the stabiliser and/or activator is present at a concentration of between 3 and 9 mg/l.

13. A composition according to any one of the preceding claims, in which the composition further comprises hydroxyl moieties.

14. A composition according to claim 13, in which the hydroxyl moieties are provided by sugars or diols.

15. A composition according to claim 13 or claim 14, in which the hydroxyl moieties are provided by 1,3 cyclohexane diol.

16. A composition according to any one of claims 13 to 15, in which the hydroxyl moieties are present at a concentration of up to 20 µg/l.

17. A composition according to any one of the preceding claims, in which the composition is buffered to an acid or neutral pH.

18. A composition according to claim 17, in which the composition is buffered to a pH of between 5 and 6.

19. A composition according to any one of the preceding claims, in which the composition further comprises collagen.

20. A composition according to claim 19, in which the collagen is present at a concentration of between 10 and 1 x 10^{15} molecules/ml.

21. A composition according to claim 19, in which the collagen is present at a concentration of between 1 x 10^{4} and 1 x 10^{14} molecules/ml.

22. A composition according to any one of the preceding claims, in which the composition further comprises a glycosaminoglycan.

23. A composition according to claim 22, in which the glycosaminoglycan is selected from the group comprising hyaluronate (D glucuronic acid N acetyl D glucosamine), chondroitin sulphate (D glucuronic acid N acetyl D galactosamine 4 or 6 sulphate), dermatan sulphate (D glucuronic acid or L iduronic acid N acetyl D galactosamine), keratan sulphate (D galactose N acetyl D glucosamine sulphate), and heparan sulphate (D glucuronic acid or L iduronic acid N acetyl D glucosamine).

24. A composition according to claim 22 or claim 23, in which the glycosaminoglycan is chondroitin -6- sulphate.

25. A composition according to any one of claims 22 to 24, in which the glycosaminoglycan is present at a concentration of between 0.1 and 1.0 mg/ml.

26. A composition according to any one of claims 22 to 24, in which the glycosaminoglycan is present at a concentration of 0.5 mg/ml.

27. A composition according to any one of the preceding claims, in which the composition is in a formulation suitable for transdermal infusion or intradermal injection.

28. A composition according to any one of the preceding claims, in which the composition is prepared a short time before administration or even immediately prior to administration.

29. A kit for preparing a composition according to any one of the preceding claims, the kit comprising an enzyme solution and an immunogen solution, the two solutions being introduced to one another and allowed to admix prior to administration to an individual in need of treatment.

30. A method of treating or preventing autoimmune conditions, the method comprising the administration of a therapeutically effective amount of a composition comprising an enzyme and an immunogen to an individual in need of treatment.

31. A method of treating, alleviating or preventing rheumatoid arthritis, the method comprising the administration of a therapeutically effective amount of a composition comprising β-glucuronidase and collagen to an individual in need of treatment.

32. The use of a therapeutically effective amount of an enzyme and an immunogen or in the preparation of a medicament for the treatment or prevention of autoimmune conditions.

33. The use of a β-glucuronidase and collagen in the preparation of a medicament for the treatment of rheumatoid arthritis.

34. A composition comprising 1,000 to 5,000 Fishman units/ml β-glucuronidase, 6 µg/ml protamine sulphate, 1µg/ml 1,3 cyclohexane diol, and 0.5 mg/ml chondroitin sulphate, buffered to pH 5.9 and a concentration of collagen selected from the group consisting of 2.5×10^{12}, 2.5×10^{10} and 2.5×10^{4} molecules/ml for use in the treatment of rheumatoid arthritis.

35. A composition substantially as hereinbefore described with reference to and as illustrated by Example 1.

ABSTRACT

A therapeutic composition for the treatment, alleviation or prophylaxis of autoimmune conditions is described. The composition comprises an enzyme and an immunogen appropriate to the condition to be treated. The composition may be given in conventional fashion but is preferably given by intradermal injection.